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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/633,423	07/31/2003	Masaya Tohyama	59150-8023.US00	3705

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EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 03/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/633,423	TOHYAMA ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-22,24-29* is/are pending in the application.

4a) Of the above claim(s) *24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,22 and 25-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *21,22 and 24-29* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/10/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's remarks and amendments filed 14 February 2006 have been entered. Claims 23 and 30 are canceled; claims 21 – 22 and 24 – 29 are pending.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

3. Claim 24 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 25 July 2005.

4. Claims 21 – 22 and 25 – 29 are under examination in the instant office action.

Withdrawn Rejections and Objections

5. The following rejections or objections made in the previous office action are withdrawn.

1) The objection to claims 25, 26, and 29 for reciting non-elected subject matter is withdrawn in light of the amendments.

2) The objection to claim 27 is withdrawn; applicant has re-written the claim in independent form.

3) The rejection of claim 29 under 35 USC 112, second paragraph is withdrawn in light of the amendments.

4) The rejection of claims 21 – 22, 25 – 26, and 28 – 29 under 35 USC 102(b) is withdrawn in light of the amendments. Claim 21 as amended now requires that the agent is bound to a PTD domain; this limitation was previously presented in claim 30.

Maintained Rejections and Objections

Claim Objections

6. Claim 28 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. This objection is maintained for the reasons of record. Applicant argues on p. 7 of the remarks that the amendment to the claim is sufficient to overcome the

objection, but claim 28 has not been amended. While claim 21 has been amended to recite "for regenerating nerves", this is an intended use and does not limit the claimed composition.

Priority

7. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

The priority document is not in English and thus the examiner cannot determine if it constitutes an enabling disclosure. The examiner has cited prior/intervening art on the claims. Therefore the effective filing date of the pending claims is the date this application was filed, 30 April 2003. It is noted that all references cited in the prior art rejections were published more than one year before the date this application and parent application 10/427,741 were filed in this country, with the exception of the reference by Bertin; the effective filing date of that reference is 26 December 2000.

Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a translation of the foreign application should be submitted under 37 CFR 1.55 in reply to this action.

Claim Rejections - 35 USC § 112

8. Claims 21 – 22 and 25 – 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide SEQ ID NO:2 or anti-p75NTR antibodies, or Pep5 with an alanine residue added to the C-terminal end, or residues 273-427 of SEQ ID NO:4, does not reasonably provide enablement for all agents, unlimited by structure, which are capable of inhibiting p75 signal transduction pathways. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection is maintained for the reasons set forth in the previous office action. Applicant argues, on p. 9 of the remarks, that because the specification discloses at least 11 specific transduction agents and at least 6 agents capable of interacting with transduction agents, the claims are enabled over their full scope. The examiner disagrees. Claim 21, as amended, requires that the composition be suitable for regenerating nerves. As all other claims require the same function, the question of whether or not the full scope of agents falling within the breadth of the claims have this function is relevant. This is a newly-added limitation, when

the claims were previously presented, claim 21 only required that the agent in the composition be capable of inhibiting a p75 pathway. While this limitation appeared in claim 23 previously, by moving the limitation to claim 21 applicant has considerably amended the scope of that claim and all dependent claims.

Agents that are transduction agents in the p75 pathway, and agents which interact with such, do not uniformly induce nerve regeneration. The art is replete with examples of agents that fall within the scope of the claims in that they either are transduction agents or interact with same, inhibit p75 signal transduction, and do not induce nerve regeneration. DeFreitas et al. (2001. J. Neurosci 21:5121-5129) teach that p75 signaling promotes neuronal survival in cultured subplate neurons (see p. 5122, first complete sentence) and that in particular NT3 and BDNF, signaling through p75, promotes survival of these cells (see p. 5123 second column). Additionally, inhibiting the p75 pathway by addition of anti-p75 Fab fragments decreases survival (see p. 5213, second column as well as Figure 3a). Salehi (2000. Neuron 27:279-288) teaches that NRAGE inhibits p75 signaling as it disrupts the p75-TrkA complex (see p. 283, figure 6), but this protein does not promote nerve regeneration, rather it promotes apoptosis (see p. 284, Figure 8). Clearly inhibition of p75 signal transduction pathways is not sufficient to regenerate nerves. Thus it improper to conclude that compositions comprising agents as claimed will be suitable for nerve regeneration. There are no structural elements common to all members of the genus of transduction agents and agents capable of interacting with these transduction agents that give the genus its nerve-regenerating properties. Thus knowing the structure of the agent is not sufficient to know that it is suitable for nerve regeneration. Furthermore knowing that the agent inhibits p75 signal transduction is also not sufficient to know whether or not the agent is suitable for nerve regeneration. Thus every agent that falls within the scope of the claims would have to be individually tested in order to determine if it can be used in a composition for regenerating nerves. Because of the very complex nature of the p75 pathway, the unpredictability of the effects of inhibiting the pathway on nerve survival and regeneration, and the lack of guidance in the specification as to the structural elements required for the agent to either be part of the pathway, an agent capable of interacting with a member of the pathway, or an agent suitable for regenerating nerves, the large degree of experimentation required by the skilled artisan in order to make and use the full scope of the claims would be undue.

Applicant argues, on p. 9 of the remarks, that there is suitable guidance in the Mukai reference to enable a skilled artisan to know which fragments of SEQ ID NO:2 work and which do not. While Mukai is on point to motifs generally, the reference is silent to SEQ ID NO:2, claimed in claim 29, and does not indicate which motifs in that protein are sufficient for nerve regeneration. Thus neither the specification nor the art provides sufficient guidance for enablement of variants and fragments as claimed.

9. Claims 21 – 22 and 25 – 29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

This rejection is maintained for the reasons of record and explained in further detail herein. Applicant argues, on p. 8 of the remarks, that the genus of agents now encompassed by claim 21 is adequately described in the specification. The examiner disagrees. Applicant is directed to the flow chart on p. 9 of the Revised Written Description Interim Guidelines Training Materials, available on the internet at <http://www.uspto.gov/web/offices/pac/writtendesc.pdf>, which is analogous to the instant situation. Claims 21 – 22 and 25 – 29 are genus claims. They are claiming any and all agents which are bound to PTD domains and which either are in the p75 transduction pathway or are capable of interacting with same. Neither the art nor the specification discloses a representative number of species falling within the genus. There are no requirements that any particular structure appear in the claimed compositions. The only requirements are functional. However knowing the functions of a molecule in this case (i.e. that it inhibits p75 transduction and is an agent in the pathway or an agent capable of interacting with same) is not sufficient to know that the agent is suitable for nerve regeneration. Thus the functional recitations are inadequate evidence that applicant was in possession of the claimed genus. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Applicant also argues that the term "fragments" is specifically defined at paragraph [0472] of US Patent Application Publication 2004/0191240. The examiner disagrees. The relevant sentence states "[v]ariants and fragments of Pep5 are also included within the definition

so long as they retain biological activity." This definition is not limiting on the size, structure, or function of the fragment. No particular amino acid sequence must be preserved. No specific biological activity must be preserved in fragments as defined here. Furthermore a different definition of fragments is provided at paragraph [0511] of the specification which allows for anywhere from 1 to n-1 amino acids, where n is the total number of amino acids in the protein. Thus the term appears to allow for essentially any single amino acid, or any sequence from SEQ ID NO:2. The specification does not provide adequate guidance to allow the skilled artisan to know, based on the amino acid sequences of SEQ ID NO:2 fragments, which ones will inhibit p75 signal transduction and whether or not they will be suitable for nerve regeneration, as it does not point out the structural elements common to all members of the genus of Pep5 fragments. Thus the claimed invention has not been adequately described.

10. Claim 28 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 28 recites the limitation "in the nerve" in line 1. There is insufficient antecedent basis for this limitation in the claim. Applicant argues that the amendment to claim 28 provides proper antecedent basis, however the claim has not been amended; the claim presented with the instant amendment is marked "original". Thus the rejection stands.

Claim Rejections - 35 USC § 102

11. Claim 27 is rejected under 35 U.S.C. 102(b) as being anticipated by Ilag (1999. Biochemical and Biophysical Research Communications 255:104-109). This rejection is maintained for the reasons of record.

Ilag teaches a protein sequence, which they call peptide 2, which is 100% identical to the protein applicant terms Pep5, i.e. SEQ ID NO:2 (see Ilag, p. 35106, first column). As the composition was administered to E. coli, it is suitable for both in vivo and in vitro administration, and thus meets the limitations of claim 27. Applicant argues that Ilag fails to teach a PTD domain. This is true, however claim 27 is an independent claim and does not recite a PTD domain.

Claim Rejections - 35 USC § 103

12. Claims 21 – 22 and 25 – 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ilag, Schwarze (1999. Science 285:1569 – 1572), Voet (Biochemistry, Second Edition, 1995. pp. 58 – 59), and Bertin (U.S. Patent Application Publication 2002/0061833, published 23 May 2002, filed 26 December 2000).

This rejection is maintained for the reasons of record. Applicant argues, on p. 13 of the remarks, that Schwarze essentially describes a method of introducing proteins into cells, and is silent as to whether or not the proteins will retain their function. Thus the reference provides a motivation to try and not a reasonable expectation of success. The examiner disagrees. Schwarze teaches that over 50 proteins were successfully transduced by attaching the TAT domain (which is a PTD, or protein transduction domain). See Schwarze, p. 1570, top of right-hand column. Schwarze teaches the method is successful in introducing the TAT-modified proteins in vitro and in vivo. Proteins delivered in this manner retain their biological activity; beta-galactosidase, which is an enzyme, remains active after being fused to TAT and injected into animals (see p. 1571). Schwarze also teaches that the method is amenable to use with therapeutic proteins (see p. 1572), because proteins that are TAT-bound as taught retain their activity. Given the teachings of Schwarze, one of ordinary skill in the art would quite reasonably expect success. Schwarze does not suggest a "try and see" approach as applicant argues, but rather teaches the applicability of the methods to proteins in general.

Applicant also argues that none of the references applied teach that PTD-bound SEQ ID NO:2 is suitable for regeneration of nerves. The examiner concedes, but notes that the claims are not drawn to methods for regeneration of nerves. Rather the recitation "for regenerating nerves", which appears in claim 21 for example, is an intended use of the claimed composition. In the previous office action the examiner clearly set forth the reason why one of ordinary skill in the art would be motivated to modify the protein from Ilag; the reason to do so would be to allow passage across the cell membrane, for inhibition of cell death as taught by Bertin.

Thus the rejection stands for the reasons of record.

Rejections Necessitated by Amendment

Claim Rejections - 35 USC §§ 102 and 103

13. Claims 21 – 22, 25 – 28 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Bredesen (US Patent Application

Publication 2004/0192889, published 30 September 2004, filed 29 March 2002, claiming benefit of provisional applications filed 29 March and 2 April 2001).

Bredesen teaches the first helix of the intracellular domain of the p75 receptor fused to TAT protein (see p. 10, paragraph [0083]). TAT protein is a PTD domain, and the p75 receptor is part of the signal transduction pathway. Thus the protein from Bredesen teaches all the structural elements of claims 21 and 27. The USPTO does not have the resources to determine if the prior art product is inherently capable of inhibiting p75 signal transduction as recited in claims 21 and 27, or if the protein is able to sufficient to accomplish the inhibition, conversion, maintenance, or enhancement as recited in claim 25 or the suppression, extinguishing, or inhibition as recited in claim 26. However rejections under 102/103 are appropriate when the prior art teaches a product that appears identical to the claimed product except that it is silent as to an inherent property. See MPEP § 2112(III).

As Bredesen teaches the protein is suitable for administration to cells, it is in a form appropriate for delivery to a neuron at a site desired for regeneration and thus meets the limitation of claim 22. As claim 28 does not limit claim 21, it is rejected for the same reasons the parent claim is rejected.

Conclusion

14. No claim is allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel E. Kolker, Ph.D.
March 17, 2006

SHARON TURNER, PH.D.
PRIMARY EXAMINER
3-22-06